CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074703

Trade Name : METOCLOPRAMIDE ORAL SOLUTION USP

Generic Name: Metoclopramide Oral Solution USP 5mg (base)/5ml

Sponsor : JVL Corp.

Approval Date: October 31, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074703

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074703

APPROVAL LETTER

ANDA 74-703

OCT 31 1997

JVL Corp.
Attention: Maurice E. Bordoni
6451 West Main Street
Morton Grove, IL 60053

Dear Sir:

This is in reference to your abbreviated new drug application dated June 28, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Metoclopramide Oral Solution USP, 5 mg (base)/5 mL.

Reference is also made to your amendments dated February 8 and 28, June 20, 1996; and July 23, September 9, and October 8, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Metoclopramide Oral Solution USP, 5 mg (base)/5 mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Reglan® Syrup, 5 mg/5 mL, of A.H. Robins Co.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center of Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074703

FINAL PRINTED LABELING

METOCLOPRAMIDE ORAL SOLUTION, USP 5 mg/5 mL
PRODUCT CODE - 7622
1 PINT (473 mL) CONTAINER LABEL

Each 5 mL (teaspoonful) contains:
Metoclopramide, USP..... 5 mg
(present as the hydrochloride)
Alcohol..... less than 0.1%
(contributed by flavorings)
In an orange-colored, palatable, aromatic, sugar-free vehicle.

N 3 60432-622-16 5

MGP

NDC 60432-622-16

METOCLOPRAMIDE

ORAL SOLUTION, USP

5 mg/5 mL

DO NOT USE THIS CONTAINER IF THE SAFETY RING AT THE BOTTOM OF THE CAP IS DETACHED OR LOOSE.

BULK CONTAINER — NOT FOR HOUSEHOLD USE

CAUTION: Federal law prohibits dispensing without prescription.

NET: 1 Pint (473 mL)

READ DISPENSING: See accompanying insert.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN. In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.
Store at controlled room temperature, 15°-30°C (59°-86°F).
Protect from freezing.
Dispense in a tight, light-resistant container as defined in the USP.
Manufactured For:
JVL Corporation
By: Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

50-7622-16
ISS. 4-96

METOCLOPRAMIDE ORAL SOLUTION, USP 5 mg/5 mL

DESCRIPTION

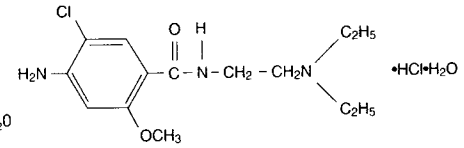
Metoclopramide Oral Solution, USP is an orange-colored, palatable, aromatic sugar-free liquid for oral administration.

Each 5 mL (teaspoonful) contains:

Metoclopramide, USP (present as the hydrochloride)	5 mg
Alcohol (contributed by flavorings)	less than 0.1%

In addition, the following inactive ingredients are present: Artificial Butterscotch Flavor; Natural & Artificial Apple Flavor; Citric Acid, USP; FD&C Yellow No. 6; Glycerin, USP; Methylparaben, NF; Propylene Glycol, USP; Propylparaben, NF; Purified Water, USP and Sorbitol Solution, USP. It may also contain Sodium Citrate, USP, for pH adjustment. The pH range is between 2.0 and 5.5.

Metoclopramide hydrochloride is a white or practically white, crystalline, odorless or practically odorless powder. It is very soluble in water, freely soluble in alcohol, sparingly soluble in chloroform, practically insoluble in ether. Chemically, it is 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Its structural formula is as follows:



$C_{14}H_{22}ClN_3O_2$•HCl•H_2O MW 354.28

CLINICAL PHARMACOLOGY

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the action of acetylcholine. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs.

Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter. It has little, if any effect on the motility of the colon or gallbladder.

In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure) single oral doses of metoclopramide produce dose-related increases in LESP. Effects begin at about 5 mg and increase through 20 mg (the largest dose tested). The increase in LESP from a 5 mg dose lasts about 45 minutes and that of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by agents like l-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions, although these are comparatively rare **(See WARNINGS)**. Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with transient fluid retention.

The onset of pharmacological action of metoclopramide is 1 to 3 minutes following an intravenous dose, 10 to 15 minutes following intramuscular administration, and 30 to 60 minutes following an oral dose; pharmacological effects persist for 1 to 2 hours.

PHARMACOKINETICS: Metoclopramide is rapidly and well absorbed. Relative to an intravenous dose of 20 mg, the absolute oral bioavailability of metoclopramide is 80% ± 15.5% as demonstrated in a crossover study. Peak plasma concentrations occur at about 1 to 2 hours after a single oral dose. Similar time to peak is observed after individual doses at steady state.

In a bioavailability study, the area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination rate remains the same. The average elimination half-life in individuals with normal renal function is 5-6 hours. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 hours. Of the 85% eliminated in the urine, about half is present as free or conjugated metoclopramide.

The drug is not extensively bound to plasma proteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg) which suggests extensive distribution of drug to the tissues.

Renal impairment affects the clearance of metoclopramide. In a study with patients with varying degrees of renal impairment, a reduction in creatinine clearance was correlated with a reduction in plasma clearance, renal clearance, non-renal clearance and increase in elimination half-life. The kinetics of metoclopramide in the presence of renal impairment remained linear however. The reduction in clearance as a result of renal impairment suggests that adjustment downward of maintenance dosage should be done to avoid drug cumulation.

INDICATIONS AND USAGE

SYMPTOMATIC GASTROESOPHAGEAL REFLUX: Metoclopramide Oral Solution is indicated as a short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy.

The principal effect of metoclopramide is on symptoms of postprandial and daytime heartburn with less observed effect on nocturnal symptoms. If symptoms are confined to particular situations, such as following the evening meal, use of metoclopramide as single doses prior to the provocative situation should be considered, rather than using the drug throughout the day. Healing of esophageal ulcers and erosions has been endoscopically demonstrated at the end of a 12-week trial using doses of 15 mg q.i.d. As there is no documented correlation between symptoms and healing of esophageal lesions, patients with documented lesions should be monitored endoscopically.

DIABETIC GASTROPARESIS (DIABETIC GASTRIC STASIS): Metoclopramide is indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The usual manifestations of delayed gastric emptying (e.g., nausea, vomiting, heartburn, persistent fullness after meals and anorexia) appear to respond to metoclopramide within different time intervals. Significant relief of nausea occurs early and continues to improve over a three-week period. Relief of vomiting and anorexia may precede the relief of abdominal fullness by one week or more.

CONTRAINDICATIONS

Metoclopramide should not be used whenever stimulation of gastrointestinal motility might be dangerous, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction or perforation.

Metoclopramide is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Such hypertensive crises may be controlled by phentolamine.

Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug.

Metoclopramide should not be used in epileptics or patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased.

WARNINGS

Mental depression has occurred in patients with and without prior history of depression. Symptoms have ranged from mild to severe and have included suicidal ideation and suicide. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the usual adult dosages of 30-40 mg/day of metoclopramide. These usually are seen during the first 24-48 hours of treatment with metoclopramide, occur more frequently in children and young adults, and are even more frequent at the higher doses. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, or dystonic reactions resembling tetanus. Rarely, dystonic reactions may present as stridor and dyspnea, possibly due to laryngospasm. If these symptoms should occur, 50 mg of diphenhydramine hydrochloride injection should be given intramuscularly, and they usually will subside. Benztropine mesylate, 1 to 2 mg intramuscularly, may also be used to reverse these reactions.

Parkinsonian-like symptoms have occurred, more commonly within the first 6 months after beginning treatment with metoclopramide, but occasionally after longer periods. These symptoms generally subside within 2-3 months following discontinuance of metoclopramide. Patients with pre-existing Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

TARDIVE DYSKINESIA: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.

Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.

PRECAUTIONS

GENERAL: In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines; hence, caution should be exercised when metoclopramide is used in patients with hypertension.

INFORMATION FOR PATIENTS: Metoclopramide may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be cautioned accordingly.

DRUG INTERACTIONS: The effects of metoclopramide on gastrointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics or tranquilizers.

The finding that metoclopramide releases catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

Absorption of drugs from the stomach may be diminished (e.g., digoxin) by metoclopramide, whereas the rate and/or extent of absorption of drugs from the small bowel may be increased (e.g., acetaminophen, tetracycline, levodopa, ethanol, cyclosporine).

Gastroparesis (gastric stasis) may be responsible for poor diabetic control in some patients. Exogenously administered insulin may begin to act before food has left the stomach and lead to hypoglycemia. Because the action of metoclopramide will influence the delivery of food to the intestines and thus the rate of absorption, insulin dosage or timing of dosage may require adjustment.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: A 77-week study was conducted in rats with oral doses up to about 40 times the maximum recommended human daily dose. Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances, such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported with prolactin-elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

An Ames mutagenicity test performed on metoclopramide was negative.

PREGNANCY: Teratogenic Effects, Pregnancy Category B: Reproduction studies performed in rats, mice and rabbits by the i.v., i.m., s.c. and oral routes at maximum levels ranging from 12 to 250 times the human dose have demonstrated no impairment of fertility or significant harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS: Metoclopramide is excreted in human milk. Caution should be exercised when metoclopramide is administered to a nursing mother.

PEDIATRIC USE: There are insufficient data to support efficacy or make dosage recommendations for metoclopramide in pediatric patients less than 18 years of age; therefore, such use is not recommended (**See OVERDOSAGE**).

ADVERSE REACTIONS

In general, the incidence of adverse reactions correlates with the dose and duration of metoclopramide administration. The following reactions have been reported, although in most instances, data do not permit an estimate of frequency.

CNS EFFECTS: Restlessness, drowsiness, fatigue and lassitude occur in approximately 10% of patients receiving the most commonly prescribed dosage of 10 mg q.i.d. (**See PRECAUTIONS**). Insomnia, headache, confusion, dizziness or mental depression with suicidal ideation (**See WARNINGS**) occur less frequently. The incidence of drowsiness is greater at higher doses. There are isolated reports of convulsive seizures without clearcut relationship to metoclopramide. Rarely, hallucinations have been reported.

EXTRAPYRAMIDAL REACTIONS (EPS): Acute dystonic reactions, the most common type of EPS associated with metoclopramide, occur in approximately 0.2% of patients (1 in 500) treated with 30 to 40 mg of metoclopramide per day. Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, opisthotonus (tetanus-like reactions) and rarely, stridor and dyspnea possibly due to laryngospasm; ordinarily these symptoms are readily reversed by diphenhydramine. (**See WARNINGS**).

Parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity and mask-like facies (**See WARNINGS**).

Tardive dyskinesia most frequently is characterized by involuntary movements of the tongue, face, mouth or jaw, and sometimes, by involuntary movements of the trunk and/or extremities; movements may be choreoathetotic in appearance (**See WARNINGS**).

Motor restlessness (akathisia) may consist of feelings of anxiety, agitation, jitteriness, and insomnia, as well as inability to sit still, pacing and foot-tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

ENDOCRINE DISTURBANCES: Galactorrhea, amenorrhea, gynecomastia, impotence secondary to hyperprolactinemia (**See PRECAUTIONS**). Fluid retention secondary to transient elevation of aldosterone (**See CLINICAL PHARMACOLOGY**).

CARDIOVASCULAR: Hypotension, hypertension, supraventricular tachycardia, and bradycardia (**See CONTRAINDICATIONS, PRECAUTIONS**).

GASTROINTESTINAL: Nausea and bowel disturbances, primarily diarrhea.

HEPATIC: Rarely, cases of hepatotoxicity, characterized by such findings as jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential.

RENAL: Urinary frequency and incontinence.

HEMATOLOGIC: A few cases of neutropenia, leukopenia or agranulocytosis, generally without clearcut relationship to metoclopramide. Methemoglobinemia, especially with overdosage of neonates (**See OVERDOSAGE**).

ALLERGIC REACTIONS: A few cases of rash, urticaria or bronchospasm, especially in patients with a history of asthma. Rarely, angioneurotic edema, including glossal or laryngeal edema.

MISCELLANEOUS: Visual disturbances. Porphyria. Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported. This potentially fatal syndrome is comprised of the symptom complex of hyperthermia, altered consciousness, muscular rigidity and autonomic dysfunction.

OVERDOSAGE

Symptoms of overdosage may include drowsiness, disorientation and extrapyramidal reactions. Anticholinergic or antiparkinson drugs or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions. Symptoms are self-limiting and usually disappear within 24 hours.

Hemodialysis removes relatively little metoclopramide, probably because of the small amounts of the drug in blood relative to tissue. Similarly, continuous ambulatory peritoneal dialysis does not remove significant amounts of drug. It is unlikely that dosage would need to be adjusted to compensate for losses through dialysis. Dialysis is not likely to be an effective method of drug removal in overdose situations.

Unintentional overdose due to misadministration has been reported in patients between the age of 2 months and 7 years with the use of metoclopramide oral solution. While there was no consistent pattern to the reports associated with these overdoses, events included seizures, extrapyramidal reactions, and lethargy.

Methemoglobinemia has occurred in premature and full-term neonates who were given overdoses of metoclopramide (1-4 mg/kg/day orally, intramuscularly or intravenously for 1-3 or more days). Methemoglobinemia has not been reported in neonates treated with 0.5 mg/kg/day in divided doses. Methemoglobinemia can be reversed by the intravenous administration of methylene blue.

DOSAGE AND ADMINISTRATION

FOR THE RELIEF OF SYMPTOMATIC GASTROESOPHAGEAL REFLUX: Administer from 10 mg to 15 mg up to q.i.d. 30 minutes before each meal and at bedtime, depending upon symptoms being treated and clinical response (**See CLINICAL PHARMACOLOGY** and **INDICATIONS AND USAGE**). If symptoms occur only intermittently or at specific times of the day, use of metoclopramide in single doses up to 20 mg prior to the provoking situation may be preferred rather than continuous treatment. Occasionally, patients (such as elderly patients) who are more sensitive to the therapeutic or adverse effects of metoclopramide will require only 5 mg per dose.

Experience with esophageal erosions and ulcerations is limited, but healing has thus far been documented in one controlled trial using q.i.d. therapy at 15 mg per dose, and this regimen should be used when lesions are present, so long as it is tolerated (**See ADVERSE REACTIONS**). Because of the poor correlation between symptoms and endoscopic appearance of the esophagus, therapy directed at esophageal lesions is best guided by endoscopic evaluation.

Therapy longer than 12 weeks has not been evaluated and cannot be recommended.

FOR THE RELIEF OF SYMPTOMS ASSOCIATED WITH DIABETIC GASTROPARESIS (DIABETIC GASTRIC STASIS): Administer 10 mg of metoclopramide 30 minutes before each meal and at bedtime for two to eight weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation.

The initial route of administration should be determined by the severity of the presenting symptoms. If only the earliest manifestations of diabetic gastric stasis are present, oral administration of metoclopramide may be initiated. However, if severe symptoms are present, therapy should begin with Metoclopramide Injection (consult labeling of the injection prior to initiating parenteral administration).

Administration of the Metoclopramide Injection up to 10 days may be required before symptoms subside, at which time oral administration may be instituted. Since diabetic gastric stasis is frequently recurrent, metoclopramide therapy should be reinstituted at the earliest manifestation.

Use in Patients with Renal or Hepatic Impairment

Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40 mL/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

See **OVERDOSAGE** section for information regarding dialysis.

Metoclopramide undergoes minimal hepatic metabolism, except for simple conjugation. Its safe use has been described in patients with advanced liver disease whose renal function was normal.

HOW SUPPLIED

Metoclopramide Oral Solution, USP 5 mg/5 mL (contains Metoclopramide, USP present as the hydrochloride) is supplied as an orange-colored, palatable, aromatic, sugar-free liquid for oral administration and is available in the following size:

Pint (473 mL)

RECOMMENDED STORAGE

Store at controlled room temperature, 15 °-30 °C (59 °-86 °F).

Protect from freezing.

Dispense in a tight, light-resistant container as defined in the USP.

CAUTION: Federal law prohibits dispensing without prescription.

Product No.: 7622

Manufactured For: JVL Corporation
By: Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

27622 ISS. 8-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074703

CHEMISTRY REVIEW(S)

D,J

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-703

3. NAME AND ADDRESS OF APPLICANT
JVL CORP.
Attention: Mr. William F. Hendershot
6451, West Main Street
Morton Grove, IL 60053

4. BASIS OF SUBMISSION
The reference listed drug is Reglan® by A.H. Robbins. Patent certification statement was provided (Vol. 1.1, p. 9). The firm states that there is no marketing exclusivity for this product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Metoclopramide Oral Solution

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original submission - 6/28/95
Refusal to file letter - 7/21/95 (FDA)
ANDA Original amendment - 8/14/95
Response to amendment with filing data - 8/28/95 (FDA)
ANDA amendment - 9/15/95
FDA requested info. for Biowaiver - 1/31/96
ANDA New correspondence for Biowaiver - 2/12/96
ANDA amendment - 3/1/96
Chemistry & labeling deficiency letter (FDA) - 3/13/96
Major amendment - 4/30/96
New correspondence - 6/20/96
Bio waiver granted - 6/26/96
Chemistry & labeling deficiency letter (FDA) #2- 8/1/96
Major amendment - 7/23/97
FAX amendment - 10/17/97

10. PHARMACOLOGICAL CATEGORY
Anti-emetic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM
Oral Solution

14. POTENCY
5 mg (base)/5 mL

15. CHEMICAL NAME AND STRUCTURE
4-Amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy-benzamide monohydrochloride monohydrate.
Mol. Wt.: 354.28

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Deficiencies are adequately addressed in the individual sections of the following review.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended.

19. REVIEWER: DATE COMPLETED:

Radhika Rajagopalan, Ph.D. 8/5/97 and 10/23/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074703

BIOEQUIVALENCE REVIEW(S)

JAN 2 2 1996

Metoclopramide Hydrochloride
5 mg/5 mL oral solution
ANDA #74-703
Reviewer: James D. Henderson
File: 74703W.695

JVL Corporation
Morton Grove, IL
Submitted:
June 28, 1995

REVIEW OF A WAIVER REQUEST

Background:

1. The sponsor submitted its original application on 6/28/95. The OGD issued a refuse to file letter on 7/21/95. The sponsor then submitted an amendment to its application on 8/14/95, and the application was found acceptable for filing on 8/15/95.

2. The sponsor describes the reference listed drug (RLD) as Reglan® Syrup 5 mg/5 mL (AH Robins, NDA #18-821, approved 3/25/83). In the Orange Book, 15th ed., 1995, p. 3-201, the RLD is listed under the dosage form heading "solution; oral".

Comments:

1. The sponsor states that the type and amount of active ingredient (AI, metoclopramide hydrochloride), conditions of use, route of administration, dosage form, strength, and labeling for metoclopramide oral solution are identical to the RLD product Reglan® Syrup.

2. The sponsor requests waiver of in vivo bioequivalence study requirements based on the following conditions of 21 CFR 320.22(b)(3):

- the test product and RLD are both oral solutions containing the same AI in the same concentration and dosage form
- The test product contains no inactive ingredient or other change in formulation from the RLD that may significantly affect absorption of the AI.

3. The test and reference product formulations are shown in Table 1. The formulations are not qualitatively identical. These differences are discussed in the footnotes to Table 1.

Deficiencies:

1. Based on the information in this submission, it appears that the two flavorings in the formulation are present in concentrations not yet approved for safety and effectiveness. Please provide evidence that the concentrations of the flavorings used in the test product formulation pose no safety problems.

2. Please show the calculations and indicate the maximum amount of [redacted](b)4 - Confidential[redacted] that is expected to be required for pH

adjustment.

Recommendation:

1. The Division of Bioequivalence does not agree that the information submitted by JVL Corporation demonstrates that metoclopramide oral solution 5 mg/5 mL falls under 21 CFR Section 320.22(b)(3) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product 5 mg/5 mL oral solution is denied.

2. The sponsor should be informed of deficiency comments 1-2 and recommendation 1.

/S/

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK

/S/ 1/22/96

JDH/gj/1-22-96/74703

cc: ANDA #74-703 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-655 (Patnaik, Henderson), Drug File, Division File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

ANDA 74-703

Food and Drug Administration
Rockville MD 20857

JUN 26 1996

JVL Corp
Attention: William F. Hendershot, Ph.D.
6451 West Main Street
Morton Grove, IL 60053

Dear Dr. Hendershot:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Metoclopramide Hydrochloride Oral Solution 5 mg/5 mL.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

(b)4 - Confidential Business

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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JUN 21 1996

Metoclopramide Hydrochloride
5 mg/5 mL oral solution
ANDA #74-703
Reviewer: James D. Henderson
File: 74703W.296

JVL Corporation
Morton Grove, IL
Submitted:
June 28, 1995

REVIEW OF A WAIVER REQUEST

Background:

1. The sponsor submitted its original application on 6/28/95. The OGD issued a refuse to file letter on 7/21/95. The sponsor then submitted an amendment to its application on 8/14/95, and the application was found acceptable for filing on 8/15/95.

2. The original application was a request for waiver of in vivo bioequivalence study requirements for the test product metoclopramide hydrochloride oral solution 5 mg/5 mL. The application was reviewed and the waiver request denied based on two deficiency comments (file date 1/22/96).

3. The sponsor describes the reference listed drug (RLD) as Reglan® Syrup 5 mg/5 mL (AH Robins, NDA #18-821, approved 3/25/83). In the Orange Book, 16th ed., 1996, p. 3-206, the RLD is listed under the dosage form heading "solution; oral".

Responses to Deficiency Comments:

1. Deficiency comment #1

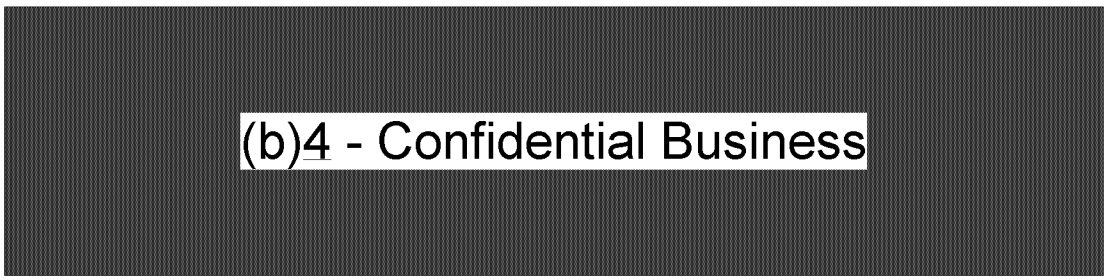
> **Based on the information in this submission, it appears that the two flavorings in the formulation are present in concentrations not yet approved for safety and effectiveness. Please provide evidence that the concentrations of the flavorings used in the test product formulation pose no safety problems.**

Sponsor's Response: The formula for this product is exactly the same as the formula for metoclopramide oral solution from Morton Grove (ANDA #70-949), approved 3/6/87. Both of the identical flavoring agents are present in the approved product from ANDA 70-949 in the same concentrations.

Reviewer's Comment: In the 2/8/96 amendment the sponsor provided a table comparing the formulations of metoclopramide oral solutions 5 mg/5 mL from ANDAs #70-949 (Morton Grove, approved product) and #74-703 (JVL, test product). The stated quantities of excipients are identical, including the two flavoring agents which were the subjects of the deficiency comment.

However, a discrepancy is now observed for the quantity of [redacted] (b)4 [redacted] for the test product ANDA #74-703. In the table from the 2/8/96 amendment, the amount is given as [redacted] (b)4 - [redacted] In

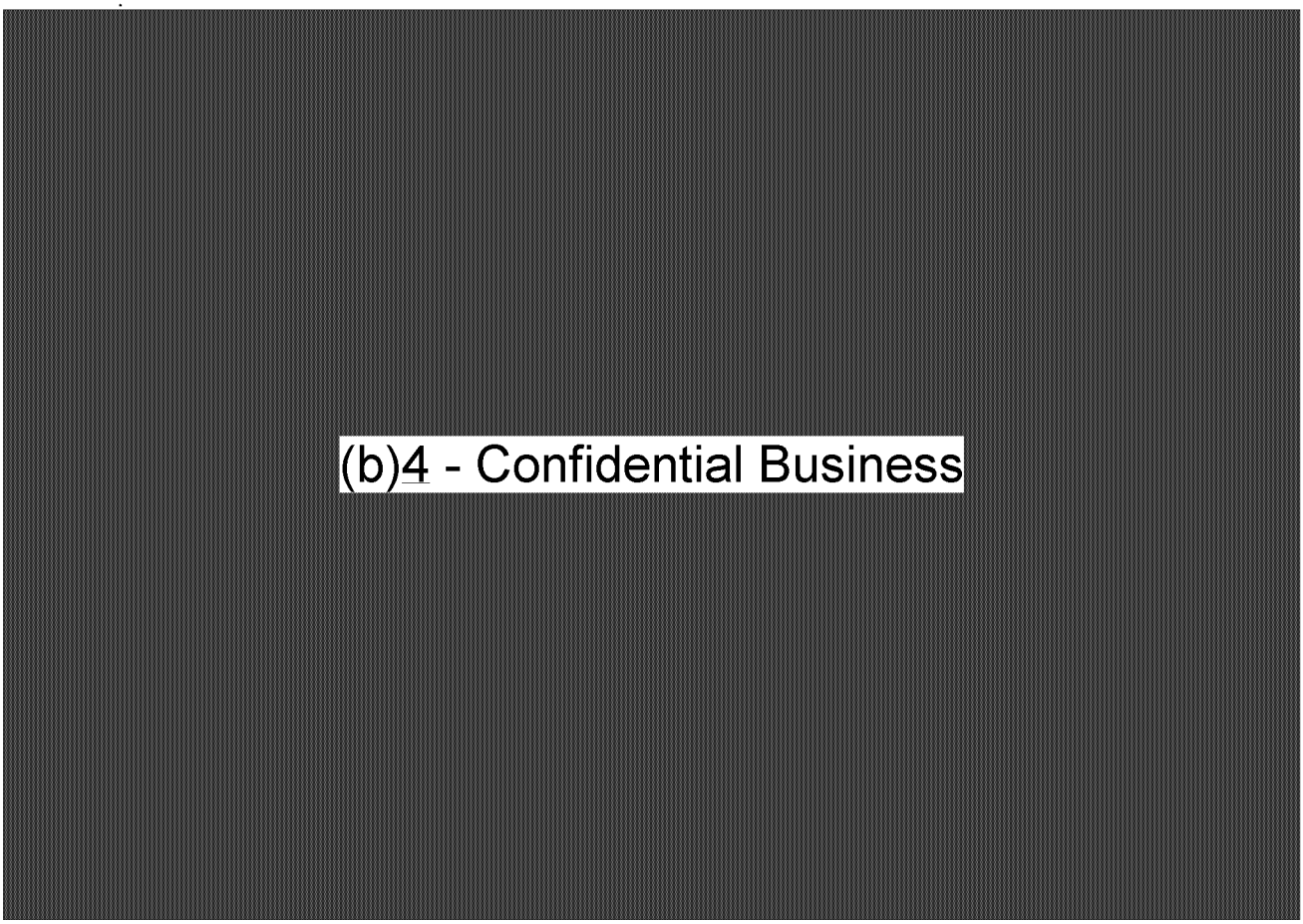
the original submission (V. 1.1, p. 41), the quantity was given as [redacted] On 6/19/96 the sponsor was contacted by telephone (transcript attached) and asked to explain this apparent discrepancy. The following explanation was provided (fax attached, to be followed with an amendment):



As shown in the previous review, the amount of citric acid in the test product is still less than that in the RLD.

2. Deficiency comment #2

Please show the calculations and indicate the maximum amount of sodium citrate solution that is expected to be required for pH adjustment.



(b)4 - Confidential Business

Conclusions:

1. The deficiency comments have been answered successfully.

2. The request for waiver of in vivo bioequivalence requirements may be granted.

Recommendations:

The Division of Bioequivalence agrees that the information submitted by JVL Corporation demonstrates that metoclopramide hydrochloride oral solution 5 mg/5 mL falls under 21 CFR Section 320.22(b)(3) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product 5 mg/5 mL oral solution is granted. From the bioequivalence point of view, the test product is deemed bioequivalent to the reference product Reglan® Syrup 5 mg/5 mL manufactured by AH Robins.

/S/

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

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6/21/1996

JDH/gj/6-21-96/74703

cc: ANDA #74-703 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-655 (Patnaik, Henderson), Drug File, Division File

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #74-703 SPONSOR: JVL
DRUG: metoclopramide hydrochloride
DOSAGE FORM: oral solution
STRENGTHS/(s): 5 mg/5 mL
TYPE OF STUDY: N/A (NOT FIRST GENERIC)

WAIVER:

The type and amount of active ingredient (metoclopramide hydrochloride), conditions of use, route of administration, dosage form, strength, and labeling for metoclopramide hydrochloride oral solution are identical to the RLD product Reglan® Syrup. The test product and RLD formulations are not qualitatively or quantitatively identical. All excipient concentrations in the test formulation appear to be within approved limits (Inactive ingredients Guide, 10/93).

Therefore, waiver of in vivo bioequivalence requirements may be granted for the test product metoclopramide hydrochloride oral solution 5 mg/5 mL under 21 CFR 320.22(b)(3).

PRIMARY REVIEWER: James D. Henderson, Ph.D. BRANCH: II
INITIAL: /S/ DATE 6-21-96

BRANCH CHIEF: Rabindra N. Patnaik, Ph.D BRANCH: II
for INITIAL: /S/ DATE 6/21/1996

DIRECTOR, DIVISION OF BIOEQUIVALENCE:
Keith K. Cha
INITIAL: /S/ DATE 6/24/96
